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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
QIAN, JANICE LI

ART UNIT	PAPER NUMBER
1632	

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DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/856,322	RAMRAKHA ET AL.
Examin r	**Art Unit**
Q. Janice Li	1632

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the corresp nd nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-32* is/are pending in the application.

4a) Of the above claim(s) *19-26,29, 30, 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,27,28 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and response filed 10/8/03 have been entered. Claims 17-32 are pending, claims 17, 18, 27, 28, and 31 have been amended. Claims 19-26, 29, 30, and 32 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 17, 18, 27, 28, and 31 are under current examination.

This application contains claims (19-26, 29, 30, and 32) drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in10/8/03 response would be addressed to the extent that they apply to current rejection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The prior rejection of claims 17 and 18 under 35 U.S.C. 101 is withdrawn in view of claim amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, 27, 28, and 31 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With respect to transfecting endothelial cells with a non-bispecific polypeptide, Applicants argue that the bi-specific polypeptide refers to binding affinity and specificity against two or more different epitopes on a cell adhesion molecule such as VCAM, thus, it is only an option whether the polypeptide is bi-specific. The argument is not persuasive in light of the teaching of the specification, particularly considering the amended claims clearly recite "*down-regulates the surface expression* of a cell adhesion molecule by the cells". According to the specification as originally filed, such surface down regulation is achieved by a fusion polypeptide (bi-specific) comprising an adhesion molecule binding region and a signaling region targeting the bounded adhesion molecule and the fusion polypeptide to an intracellular region rather than expressed on the cell surface (e.g. Specification, page 8, lines 20-29, and claim 27). However, the amended claim 17 does not require the presence of the signaling region, and the specification fails to teach how the surface expression of a cell adhesion

molecule is down regulated under such circumstance, thus, fails to provide an enabling disclosure for what is now claimed. Thus, the previous rejection stands.

With respect to whether the transfected biological tissue is suitable or enabled to be used as allografts or xenografts, Applicants argue that claim 31 has been amended to specify a method that prolongs survival of a tissue or organ graft, hence applicants do not claim a panacea that solves all the problems of xenotrasplantation, neither should that be expected of the Applicants. The argument has been fully considered but found not persuasive. This is because, the cited art of record such as *Dorling et al* and *Simon et al* clearly teach that *in vitro* down regulation of surface adhesion molecule does not correlate well with the *in vivo* beneficial effect in transplantation, thus, it is incumbent upon applicants to provide an enabling disclosure within the specification for what is now claimed. However, the specification fails to teach that the degree of expression suppression and consequently the degree of adherence reduction is sufficient to prolong the graft survival, particularly considering the volatile rejection responses as taught by *Game et al.* 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). As such, the specification fails to provide an enabling disclosure commensurate with the scope of the claims.

Applicants also argue that sufficient data has been set forth in the specification figures 9A and 9B to reasonably establish that the reduced binding of the leukocytes to the endothelial cell monolayer observed in vitro would be reproduced in vivo. In

response, the data in figures 9A and 9B appear to be obtained *in vitro*, there is nothing in these figures showing that the data would be reproduced *in vivo*, and could prolong the survival of allograft and xenograft. Particularly considering the teachings of the cited art clearly pointed out that "DOWN REGULATION OF VCAM WAS ONLY MANIFEST WHEN SUB-SATURATING DOSES WERE USED", "THE DEPENDENCE ON BOTH TIME AND DOSE OF ANTIBODY APPLIED MIGHT EXPLAIN WHY ACCOMMODATION HAS BEEN DIFFICULT TO ACHIEVE CONSISTENTLY IN *IN VIVO* MODELS OF DISCORDANT XENOTRANSPLANTATION" (*Dorling et al*). "ALTHOUGH THIS APPROACH HOLDS GREAT POTENTIAL, IT IS LIKELY THAT ORGANS DERIVED FROM SUCH ANIMALS WOULD STILL GENERATE POWERFUL IMMUNE RESPONSES IN HUMANS" (right column, page 324), and "THE EFFICACY OF MANY ADHESIVE INTERACTIONS RELEVANT TO XENOGENEIC ORGAN TRANSPLANTATION STILL REMAINS TO BE DETERMINED" (*Simon et al*). The specification fails to teach how to overcome the well-known hurdles in the art, it would have required undue experimentation for the skilled artisan intending to use the biological tissue as allograft or xenograft materials.

With respect to methods of delivery, Applicants argue that pages 9-12 of the specification provides various examples of vectors and delivery systems that are available along with various references for further consultation. The argument has been fully considered but found not persuasive because the cited pages generally and prophetically teach the required guidance, fail to specifically address issues taught in the cited art of record. For example, the claim encompasses both *ex vivo* and *in vivo* methods of delivering any type of nucleic acids by any route of administration, specifically to endothelial cells anywhere in the body, and achieving reliable expression of the polypeptide in the endothelial cells, and down-regulation of the surface

expression of a cell adhesion molecule to the extend that a therapeutic effect could be achieved, e.g. suppression of a xenograft rejection. However, *Robbins et al* teach that each type of vector system has its unique limitations, retroviral vector would not transduce cells in the quiescent stage, such as instantly claimed endothelial cells, adenoviral vectors often elicit host immune response, and herpes simplex virus can also cause immune response and significant toxicity. The specification fails to specifically address these art-known hurdles, thus fails to provide an enabling disclosure for what is now claimed. The specification contemplates using targeted delivery, and *Deonarain* teach that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). *Miller et al* teach "ONCE AGAIN, TARGETING AT THE LEVEL OF THE VECTOR HAS NOT YET BEEN PARTICULARLY WELL DEVELOPED; HENCE, LIPOSOME OR VIRAL-MEDIATED DELIVERY OF THE CFTR BEEN TO AIRWAY EPITHELIAL CELLS OF CF PATIENTS HAS RELIED LARGELY ON THE LOCALIZED DELIVERY OF THE VECTORS DIRECTLY TO THE AFFECTED TISSUES". (1st paragraph, page 198) Furthermore, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectifi d by asserting that all the disclosure related to the process is within th skill of th art.** It is the specification, not the knowledge of one skilled in the art, that must

supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Accordingly, for reasons of record and those set forth foregoing, the disclosure fails to meet the statutory enablement requirement for the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 31 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants indicated that claim 31 has been amended to specify that down regulating the surface expression of the cell adhesion molecule prolongs the survival of a tissue or organ graft. However, the method steps are still unclear with respect to how the endothelial cells in the organ grafts are transfected so that they would express the recited polypeptide since such polypeptide does not appear to be naturally exist in the recited tissue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claim 17 under 35 U.S.C. 102(b) as being anticipated by *Klein et al* ((Eur J Cell Bio 1997;72(S43):101)) is withdrawn in view of claim amendment.

The prior rejection of claim 17 under 35 U.S.C. 102(b) as being anticipated by *Orosz et al* (Transplant 1993; 56:453-60, IDS/2) is withdrawn in view of claim amendment.

The prior rejection of claims 27 and 28 under 35 U.S.C. 102(b) as being anticipated by *Greenman et al* (J Immunol Meth 1996;194:169-180, IDS/21) is withdrawn in view of claim amendment.

The prior rejection of claims 27 and 28 under 35 U.S.C. 102(b) as being anticipated by *Yuan et al* (Biochem J 1996;318:591-6, IDS/23) is withdrawn in view of claim amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 18, 27, and 28 stand or newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Greenman et al* (J Immunol Meth 1996;194:169-180, IDS/21), in view of *Klein et al* ((Eur J Cell Bio 1997;72(S43):101)) and .

Greenman et al teach expressing a fusion polypeptide in CHO cell, wherein the fusion polypeptide comprising a single-chain antibody fragment with specific binding affinity for CD2 (a cell adhesion molecule), and a signaling region for subcellular targeting (NSEKDEL, right column, page 171), whereby, the expression of cell surface molecules was inhibited (e.g. table 2). They go on to teach that the general approach of intracellular single chain antibody expression provides a simple, efficient way of studying the function of molecules that can not be studied by current techniques such as transgenic or knockout mice, because molecules of interest can be deleted in a controlled manner without genetic modification, that the skilled artisans have used this approach in various cell types of human, yeast, and xenopus (page 170). *Greenman et al* do not express the polypeptide in endothelial cells.

Klein et al teach that various cultivated endothelial cells (HUVEC, HAFEC, WBC-EC) are available for investigating surface expression of adhesion molecules (VCAM-1, ICAM-1), and desirability for studying endothelial cells as well as the role of adhesion

molecules in these cells because they are "A POWERFUL TOOL IN STUDYING PROCESSES OF PATHOGENESIS, E.G. INFLAMMATION, ATHEROSCLEAROSIS, HYPOXAEMIA AND REPERFUSION".

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Greenman et al* by simply substituting the CHO cell with endothelial cells as taught by *Klein et al* and obtaining a collection of endothelial cells with reduced surface expression of a cell adhesion molecule with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention for the cell type of interests and molecules of interests because the method provides a simple and efficient technique for studying the function of molecules in a particular cell type. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants argue that *Greenman* teaches that the inhibition of CD2 was not complete or straightforward, thus there is no reasonable expectation of success. *Klein* is merely an abstract describing experiments where endothelial cells were exposed to different oxygen tensions and effects of such conditions on the expression of certain cell adhesion molecules. Klein does not inhibit the expression of those CAMs nor does he ever suggest that it might be desirable to do so.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the reference of *Greenman et al* is relied upon as a showing

that the skilled in the art knows to suppress surface expression of adhesion molecules by employing a fusion polypeptide targeting the surface expressed adhesion molecule to a subcellular location, thus, inhibiting the expression of the adhesion molecule. The reference of *Klein et al* is relied upon as a showing that the skilled artisan knows the importance of endothelial cells and their association with CAM adhesion molecules, and the desirability to study the role or function of the adhesion molecules in these cells. In response to applicant's argument that there is not suggestion to combine the reference, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Furthermore, there is no limitation on the degree of expression reduction in these claims, thus, even though *Greenman et al* acknowledge that the inhibition is incomplete, such acknowledgement only reflects the state of the art with respect to whether the cells are suitable for clinical use, it does not affect the validity of the reference for the purpose of the recited combined teaching. Thus, the reference still stands.

The prior rejection of claims 17, 18, and 31 under 35 U.S.C. 103(a) as being unpatentable over *Yuan et al* (Biochem J 1996;318:591-6, IDS/23), in view of *Dorling et al* (Transplant 1996;62:1127-36, IDS/8) is withdrawn in view of claim amendment and

because Yuan et al teach a fusion polypeptide that is not directly binding to adhesion molecule but rather its ligand.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers

for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
January 8, 2004

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER